growth hormone variant has vertebrate growth hormone inhibitory activity, with the proviso that said variant does not correspond to human growth hormone with all of the following substitutions and no others: Y111V, L113I, K115E, D116Q, E118K, E119R, G120L, Q122E, T123G, G126L, R127I and E129S.

H1 Cont

114 (amended). A non-naturally occurring DNA molecule encoding a vertebrate growth hormone variant, said variant having an amino acid sequence comprising a substitution of any amino acid other than glycine or alanine at the glycine corresponding to Gly119 of bovine growth hormone, wherein said variant has growth hormone inhibitory activity, with the proviso that said variant does not correspond to human growth hormone with all of the following substitutions and no others: Y111V, L113I, K115E, D116Q, E118K, E119R, G120L, Q122E, T123G, G126L, R127I and E129S.

H2

REMARKS

1. To narrow the issues, the gene therapy claims (63, 88-98) have been cancelled.

2. Supervisory Patent Examiner Gary Kunz advised us of an antecedent basis problem in claims 107 and 114. This has now been corrected. It is our understanding that with these amendments, claim 107-117 are allowable.

3. Issues remain as to the following sets of claims:

(a) claim 10 (and dependent claims 11-28, 34, 37-45, 75-80, 99)

(b) claim 29 (and dependent claims 30-33, 65 and 74)

(c) claim 66 (and dependent claims 67-73)

(d) claim 81 (and dependent claims 82-87, 89, 100-106).

Claim 10, as originally presented (March 14, 1997), closely paralleled claim 49 of allowed application 313,505, which became claim 2 of USP 5,681,809. It was to "a purified or non-naturally occurring DNA molecule comprising a coding sequence encoding" the polypeptide of claim 2 of the '809 patent.

For convenience, we essentially reiterate the explanation of claim 10 (as originally presented) as given on pp. 13-15 of our March 14, 1997 amendment.

Claim 10 is a generic claim to a DNA molecule encoding a polypeptide with growth hormone receptor antagonist activity. This new polypeptide is defined so as to be, either, in essence, the polypeptide recited in a patented claim (claim 1 of USP 5,350,836) or the polypeptide recited in an allowed claim (claim 49 of 08/313,505)[1]. Claim 1 of the '836 patent covered

> A vertebrate growth hormone in which the amino acid position in said vertebrate growth hormone corresponding to amino acid Gly 119 of bovine growth hormone is deleted or substituted with an amino acid, said vertebrate growth hormone having growth hormone antagonist activity.

Thus, it covers all single substitution mutants of vertebrate growth hormones wherein the mutation was at the residue corresponding to bGH Gly119.

Claim 49 of 08/313,505 was written to avoid overlap with claim 1 of the '836 patent, in that it required a difference from a first reference vertebrate growth hormone "at one or more of the remaining amino acid positions", i.e., positions other than the one corresponding to bGH 119. Claim 49 read as follows:

> A polypeptide which comprises an amino acid sequence which
>
> (A) is at least 50% identical with the sequence of a first reference vertebrate growth hormone, and
>
> (B) differs therefrom solely in that
>
> (I) the amino acid position corresponding to amino acid Gly119 of bovine growth hormone is substituted with an amino acid other than alanine, and either

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[1] Now claim 2 of USP 5,681,809.

(II) at one or more of the remaining amino acid positions it is characterized by

(a) a substitution of a conservative replacement amino acid for the corresponding first reference vertebrate growth hormone residue, or

(b) a substitution of a non-conservative replacement amino acid for the corresponding first reference vertebrate growth hormone residue where

(i) a second reference vertebrate growth hormone exists for which the corresponding amino acid is a non-conservative substitution for the corresponding first reference vertebrate growth hormone residue, and/or

(ii) the binding affinity for the first reference vertebrate growth hormone's receptor of a single substitution mutant of the first reference vertebrate growth hormone, wherein said corresponding residue, which is not alanine, is replaced by alanine, is at least 10% of the binding affinity of the wild-type first reference vertebrate growth hormone,

or

(III) it differs from the sequence of said first reference hormone by (a) one or more deletions of residues which are not part of the alpha helixes of said reference vertebrate growth hormone corresponding to helices 1(7-34), 2(75-87), 3(106-127) and 4(152-183) of porcine growth hormone, each deleted residue furthermore not being a conserved residue in the vertebrate GH family, or (b) one or more deletions of residues found in said first reference vertebrate growth hormone but deleted in a second reference vertebrate growth hormone,

or both (II) and (III);
said polypeptide having growth hormone receptor antagonist activity.

Claim 10 covers DNA molecules encoding both sorts of polypeptides, i.e., those encoding the single substitution mutants of claim 1 of the '836 patent, and DNA molecules encoding the multiple substitution mutants of claim 49 of the '505 application, now claim 2 of the '809 patent.[2] Note that paragraphs (B)(II)(c) and (B)(II)(d) of claim 10 correspond to (III)(a) and (III)(b) of claim 2 of the '809 patent.

Since claim 10 is drawn to a DNA molecule encoding either a polypeptide which is the subject of an '836 patent claim, or one which is the subject of an '809 patent claim (save for its omission of one embodiment of the '836 claim), it is clear that it must be considered patentable as well, for the reasons developed during the prosecution of the '836 and '809 patents. We wish to note that claim 49 of the '505 application was approved of, not only by Examiner Carlson, but also by SPE Vasu Jagannathan, BPS Richard Schwartz, and QCS Robert Hill. Full faith and credit[3] should be given to the finding that the polypeptides of claim 1 of USP 5,350,836 and claim 2 of the '809 patent are patentable. Since designing DNA encoding such polypeptides is straightforward (see specification, p. 30), there is no reason to reject the new claims for lack of enablement,

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[2] However, the polypeptide recited in new claim 9 differs from that of claim 1 of the '836 patent in that it does not include mutants in which the bGH G119 equivalent is deleted.

[3] MPEP §704, "Previous Examiner's Search", provides that an examiner who takes over an application is to give "full faith and credit" to the search and action of the prior examiner. To the extent that common issues are raised, sound administration justifies a similar practice vis-a-vis prosecution of a daughter application.

lack of description or indefiniteness.

On January 22, 1998, claim 10 was amended to (1) insert --a growth hormone receptor antagonist which is--, between "encoding" and "a polypeptide", and (2) to add what we have referred to in prosecution as the "Cunningham proviso".

As a result, the polypeptide limitations of claim 10 were essentially identical to the polypeptide of **claim 1 of USP 5,958,879**, which issued on a continuation of the '505 application.

The rationale of the "Cunningham proviso" of '879 claim 1, as imported into the instant claims, is explained at pp. 12-14 of the January 22, 1998 Amendment. Examiner Saoud has since accepted the propriety of the "Cunningham proviso", witness, e.g., page 6, line 11 of the January 2, 2002 office action.

On July 28, 2000, to assuage Examiner's concerns (we think, misplaced) concerning the words "reference", "first reference" and "second reference" (despite their acceptance in the '809 and '879 prosecutions), we changed "reference" and "first reference" to --first--, and "second reference" to --second--.

Finally, on May 8, 2002, at the Examiner's request, we excised "purified and" from the preamble of claim 10.

Claim 29, as first presented, paralleled **'809 claim 26**. Amendments were made to claim 29 which paralleled those made to claim 10. In addition, in response to the Examiner's concern, we amended claim 29 on November 8, 1999 to require that the polypeptide include residues corresponding to residues 96-133 (a known active fragment) of bovine growth hormone.

Claim 66 differs from claim 10 in that, instead of reciting the "Cunningham proviso", it requires that the first and second reference vertebrate GHs are mammalian GHs. This is an independent basis for distinguishing Cunningham.

Claim 81 was presented in response to claim language suggested by the examiner. Claims 107-117 adhere more closely

to the Examiner's suggestion.

If the POT sees fit to allow claims 10 and 29 (and their dependent claims), we would be willing to cancel claims 81-97, 89 and 100-106.

We do not know which of the description, enablement and indefiniteness issues raised previously are still in contention. The Examiner's attention is respectfully directed to pp. 7-14 of the May 8, 2002 amendment.

In addition, please see the discussion of "description" issues at pp. 14-24 of our July 28, 2000 amendment, and of "enablement" at pp. 4-10 of our November 8, 1999 amendment, pp. 7-11 of our September 10, 1998 amendment, and pp. 15-22 of our January 22, 1998 amendment.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

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USSN - 08/488,164

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claims 107 and 114 have been amended as follows:

107 (twice amended). A non-naturally occurring DNA molecule comprising a coding sequence encoding a vertebrate growth hormone variant comprising an amino acid substitution of an amino acid, other than glycine or alanine, for the amino acid of said vertebrate growth hormone at the position corresponding to the glycine at position 119 of bovine growth hormone, wherein the growth hormone variant has vertebrate growth hormone inhibitory activity, with the proviso that said [polypeptide] variant does not correspond to human growth hormone with all of the following substitutions and no others: Y111V, L113I, K115E, D116Q, E118K, E119R, G120L, Q122E, T123G, G126L, R127I and E129S.

114 (amended). A non-naturally occurring DNA molecule encoding a vertebrate growth hormone variant, said variant having an amino acid sequence comprising a substitution of any amino acid other than glycine or alanine at the glycine corresponding to Gly119 of bovine growth hormone, wherein said variant has growth hormone inhibitory activity, with the proviso that said [polypeptide] variant does not correspond to human growth hormone with all of the following substitutions and no others: Y111V, L113I, K115E, D116Q, E118K, E119R, G120L, Q122E, T123G, G126L, R127I and E129S.

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